

Gene Section

Review

SMYD3 (SET and MYND domain containing 3)

Xue-Gang Luo, Shu Guo, Tong-Cun Zhang

College of Bioengineering, Tianjin University of Science and Technology, Tianjin, China (XGL, SG, TCZ)

Published in Atlas Database: July 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/SMYD3ID46100ch1q44.html>

DOI: 10.4267/2042/44998

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2011 *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

Identity

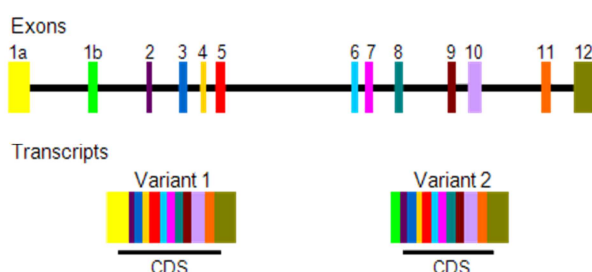
Other names: FLJ21080, KMT3E, MGC104324, ZMYND1, ZNFN3A1, bA74P14.1

HGNC (Hugo): SMYD3

Location: 1q44

Local order: The human SMYD3 gene maps on 1q44 between the LOC100132379 and the KIF26B loci.

DNA/RNA



Genomic organization of SMYD3. The SMYD3 gene is comprised of 12 exons and encodes for two alternatively transcript variants that use different first exon and promoter.

Description

The SMYD3 gene is comprised of 12 exons, spanning 757.8 kb on chromosome 1q44. Two transcript variants were encoded using different first exon and promoter. A variable number of tandem repeats (VNTR) polymorphism in E2F-1-binding element in the promoter region of SMYD3 transcript variant 1 has

been shown to be significantly associated with an increased risk of colorectal cancer, hepatocellular carcinoma and breast cancer in Japanese population (Tsuge et al., 2005). It is also shown that this VNTR polymorphism might be a susceptibility factor for human esophageal squamous cell carcinoma in relation to tobacco smoking (Wang H et al., 2008). However, it seemed that this polymorphism was not associated with the cancer risk in all the races in the world (Frank et al., 2006; Wang et al., 2007).

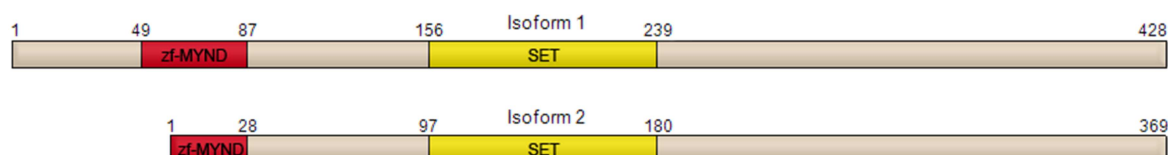
A copy-number variation (CNV) on chromosome 1 was observed to be proximal to SMYD3 that displayed high expression in the lymphoblastoid cell lines, and this CNV was significantly associated with 1-beta-D-arabinofuranosylcytosine cytotoxicity (Kalari et al., 2010).

Transcription

The SMYD3 gene mainly has two transcript variants of 1641 and 1469 bp, each comprising 12 exons. They differ for the alternative usage of the different first exon and promoter. The variant 2 is shorter at the N-terminus, compared to the variant 1. Besides, there was a report showed that another SMYD3 transcript variant, termed SMYD3-NY, was detected in adult human testis and spermatozoa using the methods of hybridization with a human cDNA microarray (Zhou et al., 2005). However, SMYD3-NY has not been further confirmed with experimental evidence yet.

Pseudogene

Not yet described.



Protein domains of SMYD3. SMYD3 has two isoforms. The isoform 2 (369 amino acids) just lacks 59 amino acid at the N-terminus of the isoform 1 (428 amino acids).

Protein

Description

The 1641 bp transcript variant 1 encodes a 428 amino acids protein containing a zf-MYND domain (49-87) and a SET domain (148-239), the transcript variant 2 uses a downstream translational start codon and encodes a 369 amino acids protein which is 100% identical with the 60-428 region of the isoform 1.

It has been shown that human cancer cells also express a cleaved form of SMYD3 lacking the 34 amino acids in the N-terminal region of the full-length SMYD3 isoform 1. It seems that the N-terminal region of SMYD3 isoform 1 plays an important role for the regulation of its methyltransferase activity, and the cleavage of 34 amino acids in the N-terminal region or interaction with heat shock protein 90 alpha (HSP90alpha) may enhance the histone methyltransferase (HMTase) activity compared to the full-length protein (Silva et al., 2008).

Expression

SMYD3 is frequently up-regulated in colorectal carcinoma, hepatocellular carcinoma and breast cancer (Hamamoto et al., 2004; Hamamoto et al., 2006). miR-124 can down-regulate SMYD3 through binding to 3' UTR of SMYD3 protein (Furuta et al., 2010).

Localisation

The SMYD3 protein is located mainly in the cytoplasm when the cells are arrested at G0/G1, but accumulated in the nuclei at S phase and G2/M (Hamamoto et al., 2004).

Function

SMYD3 is a SET-domain-containing lysine histone methyltransferase which has been regarded as an important factor in carcinogenesis. Formed a complex with RNA polymerase II through an interaction with the RNA helicase HELZ, SMYD3 specifically methylates histone H3 at lysine 4 and activates the transcription of a set of downstream genes (including of Nkx2.8, hTERT, WNT10B, VEGFR1, c-Met, etc) containing a "5' - CCCTCC - 3'" or "5' - GGAGGG - 3'" sequence in the promoter region, and these activities require protein cofactors HSP90alpha (Hamamoto et al., 2004; Liu et al., 2007; Hamamoto et al., 2006; Kunizaki et al., 2007; Zou et al., 2009). Enhanced expression of SMYD3 is essential for the growth of many cancer cells (such as colorectal carcinoma, hepatocellular carcinoma, breast cancer, etc), and it also could stimulate cell adhesion and migration, whereas suppression of SMYD3 by RNAi or other reagents induces apoptosis and inhibits cell proliferation and migration (Hamamoto et al., 2004; Hamamoto et al., 2006; Luo et al., 2007; Wang SZ et al., 2008; Zou et al., 2009; Chen et al., 2007; Luo et al., 2010).

SMYD3 may be an important coactivator of estrogen

receptor (ER) in the estrogen signal pathway. It can directly interact with the ligand binding domain of ER, in turn augments ER target gene expression via histone H3-K4 methylation (Kim et al., 2009). Besides, it has been shown that SMYD3 could interact with Jab1 in yeast cells and in vitro, and might be required for Jab1-mediated enhancement of hemopoietic progenitors cells (Mori et al., 2008).

Homology

SMYD3 displays structural homologies with other members of the SMYD histone methyltransferase family, such as the SMYD1 (30% identity, 50% similarity), SMYD2 (32% identity, 52% similarity), SMYD4 and SMYD5.

Mutations

Note

Not yet described. A VNTR polymorphism in the 5' flanking region of SMYD3 has been reported as we mentioned in the "DNA Description" section.

Implicated in

Colorectal carcinoma

Note

SMYD3 expression is markedly elevated in colorectal cancers, and this upregulation enhances the growth of tumor cells (Hamamoto et al., 2004).

Hepatocellular carcinoma

Note

SMYD3 was found to be overexpressed in human hepatocarcinoma cells, and silencing of SMYD3 by RNAi could inhibit cell proliferation and migration (Hamamoto et al., 2004; Zou et al., 2009; Chen et al., 2007). miR-124, usually be epigenetically silenced in hepatocarcinoma cells, could downregulate SMYD3 expression and inhibit cell growth (Furuta et al., 2010). Hepatitis B virus X protein could upregulate SMYD3 expression in HepG2 hepatocellular carcinoma cell lines, and this effect might promote the progress of hepatoma (Yang et al., 2009).

Breast cancer

Note

SMYD3 overexpression was observed in the great majority of breast cancer tissues, and suppression of SMYD3 by RNAi or other reagents could inhibit cell proliferation and migration (Hamamoto et al., 2006; Luo et al., 2010). Furthermore, SMYD3 was identified as a new coactivator for ER and was required in estrogen signal pathway (Kim et al., 2009).

Cervical carcinoma

Note

Suppression of SMYD3 by RNAi could reduce cell proliferation, colony formation and migration/invasion

activity, and induces apoptosis in Hela cervical carcinoma cells (Wang SZ et al., 2008).

Multiple myeloma

Note

Triptolide, an antitumor Chinese herb extracted ingredient, could decrease the expression of SMYD3 and inhibit the proliferation of multiple myeloma cell line U266 in a time- and dose-dependent manner (Zhao et al., 2010).

Esophageal squamous cell carcinoma

Note

A VNTR polymorphism in E2F-1-binding element in the promoter region of SMYD3 transcript variant 1 was observed to be a susceptibility factor for human esophageal squamous cell carcinoma in relation to tobacco smoking (Wang H et al., 2008).

Breakpoints

Note

A breakpoint on 1q44 is located in the SMYD3 gene (Aktas et al., 2010).

References

- Hamamoto R, Furukawa Y, Morita M, Iimura Y, Silva FP, Li M, Yagyu R, Nakamura Y. SMYD3 encodes a histone methyltransferase involved in the proliferation of cancer cells. *Nat Cell Biol.* 2004 Aug;6(8):731-40
- Tsuge M, Hamamoto R, Silva FP, Ohnishi Y, Chayama K, Kamatani N, Furukawa Y, Nakamura Y. A variable number of tandem repeats polymorphism in an E2F-1 binding element in the 5' flanking region of SMYD3 is a risk factor for human cancers. *Nat Genet.* 2005 Oct;37(10):1104-7
- Zhou Z, Ren X, Huang X, Lu L, Xu M, Yin L, Li J, Sha J. SMYD3-NY, a novel SMYD3 mRNA transcript variant, may have a role in human spermatogenesis. *Ann Clin Lab Sci.* 2005 Summer;35(3):270-7
- Frank B, Hemminki K, Wappenschmidt B, Klaes R, Meindl A, Schmutzler RK, Bugert P, Untch M, Bartram CR, Burwinkel B. Variable number of tandem repeats polymorphism in the SMYD3 promoter region and the risk of familial breast cancer. *Int J Cancer.* 2006 Jun 1;118(11):2917-8
- Hamamoto R, Silva FP, Tsuge M, Nishidate T, Katagiri T, Nakamura Y, Furukawa Y. Enhanced SMYD3 expression is essential for the growth of breast cancer cells. *Cancer Sci.* 2006 Feb;97(2):113-8
- Chen LB, Xu JY, Yang Z, Wang GB. Silencing SMYD3 in hepatoma demethylates RIZ1 promoter induces apoptosis and inhibits cell proliferation and migration. *World J Gastroenterol.* 2007 Nov 21;13(43):5718-24
- Kunizaki M, Hamamoto R, Silva FP, Yamaguchi K, Nagayasu T, Shibuya M, Nakamura Y, Furukawa Y. The lysine 831 of vascular endothelial growth factor receptor 1 is a novel target of methylation by SMYD3. *Cancer Res.* 2007 Nov 15;67(22):10759-65
- Liu C, Fang X, Ge Z, Jalink M, Kyo S, Björkholm M, Gruber A, Sjöberg J, Xu D. The telomerase reverse transcriptase (hTERT) gene is a direct target of the histone methyltransferase SMYD3. *Cancer Res.* 2007 Mar 15;67(6):2626-31
- Luo XG, Ding Y, Zhou QF, Ye L, Wang SZ, Xi T. SET and MYND domain-containing protein 3 decreases sensitivity to dexamethasone and stimulates cell adhesion and migration in NIH3T3 cells. *J Biosci Bioeng.* 2007 May;103(5):444-50
- Wang XQ, Miao X, Cai Q, Garcia-Barcelo MM, Fan ST. SMYD3 tandem repeats polymorphism is not associated with the occurrence and metastasis of hepatocellular carcinoma in a Chinese population. *Exp Oncol.* 2007 Mar;29(1):71-3
- Mori M, Yoneda-Kato N, Yoshida A, Kato JY. Stable form of JAB1 enhances proliferation and maintenance of hematopoietic progenitors. *J Biol Chem.* 2008 Oct 24;283(43):29011-21
- Silva FP, Hamamoto R, Kunizaki M, Tsuge M, Nakamura Y, Furukawa Y. Enhanced methyltransferase activity of SMYD3 by the cleavage of its N-terminal region in human cancer cells. *Oncogene.* 2008 Apr 24;27(19):2686-92
- Wang H, Liu Y, Tan W, Zhang Y, Zhao N, Jiang Y, Lin C, Hao B, Zhao D, Qian J, Lu D, Jin L, Wei Q, Lin D, He F. Association of the variable number of tandem repeats polymorphism in the promoter region of the SMYD3 gene with risk of esophageal squamous cell carcinoma in relation to tobacco smoking. *Cancer Sci.* 2008 Apr;99(4):787-91
- Wang SZ, Luo XG, Shen J, Zou JN, Lu YH, Xi T. Knockdown of SMYD3 by RNA interference inhibits cervical carcinoma cell growth and invasion in vitro. *BMB Rep.* 2008 Apr 30;41(4):294-9
- Kim H, Heo K, Kim JH, Kim K, Choi J, An W. Requirement of histone methyltransferase SMYD3 for estrogen receptor-mediated transcription. *J Biol Chem.* 2009 Jul 24;284(30):19867-77
- Yang L, He J, Chen L, Wang G. Hepatitis B virus X protein upregulates expression of SMYD3 and C-MYC in HepG2 cells. *Med Oncol.* 2009 Dec;26(4):445-51
- Zou JN, Wang SZ, Yang JS, Luo XG, Xie JH, Xi T. Knockdown of SMYD3 by RNA interference down-regulates c-Met expression and inhibits cells migration and invasion induced by HGF. *Cancer Lett.* 2009 Jul 18;280(1):78-85
- Aktas D, Utine EG, Mrasek K, Weise A, von Eggeling F, Yalaz K, Posorski N, Akarsu N, Alikasifoglu M, Liehr T, Tuncbilek E. Derivative chromosome 1 and GLUT1 deficiency syndrome in a sibling pair. *Mol Cytogenet.* 2010 May 28;3(1):10
- Furuta M, Kozaki KI, Tanaka S, Arai S, Imoto I, Inazawa J. miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. *Carcinogenesis.* 2010 May;31(5):766-76
- Kalari KR, Hebring SJ, Chai HS, Li L, Kocher JP, Wang L, Weinshilboum RM. Copy number variation and cytidine analogue cytotoxicity: a genome-wide association approach. *BMC Genomics.* 2010 Jun 4;11:357
- Luo XG, Zou JN, Wang SZ, Zhang TC, Xi T. Novobiocin decreases SMYD3 expression and inhibits the migration of MDA-MB-231 human breast cancer cells. *IUBMB Life.* 2010 Mar;62(3):194-9
- Zhao F, Chen Y, Zeng L, Li R, Zeng R, Wen L, Liu Y, Zhang C. Role of triptolide in cell proliferation, cell cycle arrest, apoptosis and histone methylation in multiple myeloma U266 cells. *Eur J Pharmacol.* 2010 Nov 10;646(1-3):1-11

This article should be referenced as such:

Luo XG, Guo S, Zhang TC. SMYD3 (SET and MYND domain containing 3). *Atlas Genet Cytogenet Oncol Haematol.* 2011; 15(4):344-346.
